PATENT COOPERATION TREATY

5 DEC. 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02.12.2005

Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
14673/PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/002165	30.06.2004	30.06.2003

Applicant
UNIVERSITE DE LAUSANNE et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 14673/PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/002165	International filing date *(day/month/year)* 30.06.2004	Priority date *(day/month/year)* 30.06.2003

International Patent Classification (IPC) or national classification and IPC
C07K14/47, C12N15/12, A61K47/42, A61K38/17, A61P35/00

Applicant
UNIVERSITE DE LAUSANNE et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31.03.2005	02.12.2005

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/002165

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-31	as originally filed

Sequence listings part of the description, Pages

1-6	received on 01.10.2004 with letter of 28.09.2004

Claims, Numbers

1-30	received on 04.11.2005 with letter of 01.11.2005

Drawings, Sheets

1/8-8/8	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 25-28 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. claims 25-28 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-30
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-24, 29, 30
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

1. Claims **25-28** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

2. The following documents are referred to in this communication:

D1 : WO 94/03597 A (DUCHESNE MARC ; TOCQUE BRUNO (FR); RHONE POULENC RORER SA (FR); SCHWEI) 17 February 1994 (1994-02-17)

D2 : WO 03/018630 A (FRENCH JULIET ; KENNEDY DEREK (AU); UNIV GRIFFITH (AU); HART DEREK (AU) 6 March 2003 (2003-03-06)

D3 : DUCHESNE M ET AL: "Identification of the SH3 domain of GAP as an essential sequence for Ras_GAP-mediated signaling" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 259, 22 January 1993 (1993-01-22), pages 525-528, XP002092187 ISSN: 0036-8075

D4 : YANG JIANG-YAN ET AL: "Antiapoptotic signaling generated by caspase-induced cleavage of RasGAP" MOLECULAR AND CELLULAR BIOLOGY, vol. 21, no. 16, August 2001 (2001-08), pages 5346-5358, XP002296743 ISSN: 0270-7306

D5: LEBLANC VERONIQUE ET AL: "Ras-GTPase activating protein inhibition specifically induces apoptosis of tumour cells" ONCOGENE, vol. 18, no. 34, August 1999 (1999-08), pages 4884-4889, XP002296744 ISSN: 0950-9232

D6: SCHWARZE S ET AL: "In vivo protein transduction: delivery of a biologically active protein into the mouse" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 285, no. 5433, 3 September 1999 (1999-09-03), pages 1569-1572, XP002140133 ISSN: 0036-8075

The present application concerns the finding that a peptide comprising a fragment of the N2 sequence of the RasGap protein, said peptide comprising at least the sequence WMWVTNLRTD, enhance the ability of genotoxins to kill selectively cancer cells.

3. **IMPORTANT CLARITY, SUPPORT AND SUFFICIENCY OF DISCLOSURE OBJECTIONS** (Art. 6, 5 PCT)

3.1 Claim 1 contains several unclear terms:

3.1.1 The term "**variants thereof**" is unclear because it is not obvious whether said variants refer to (a) the peptide claimed, (b) the N2 sequence, (c) the RasGap protein or (d) the amino acid sequence WXWVTXXRTX. If the variants refers to (a), (b) or (c) then, the complete N2 sequence of RasGap also falls under the scope of protection and D4 is novelty destroying for the subject-matter of claim 1. In the case the variants refer to WXWVTXXRTX, no support is found in the application for such variants. It appears however, that, in view of the description, said variants refer to those peptides comprising WXWVTXXRTX, wherein X is an amino acid; in such case the expression "variants thereof" is not necessary. The opinion on novelty and inventive step of the international authority is given taking into consideration such interpretation.

3.1.2 The expression "**a peptide shorter than the N2 sequence of RasGap**" is considered unclear in the sense of Art 6 PCT. First, because it does not refer to fragments of the N2 sequence of the RasGap protein, which was the subject-matter originally claimed and which has support in the application. Second, said expression merely reflects a size limitation of a peptide, but it is not formulated in clear terms (e.g. sequence length of the peptide in number of amino acids).

3.2 Due to the broad definition of the term "a variants thereof" in claim 1, the only technical feature remaining in the main claim is a functional definition, namely that the peptide should enhance the ability of a genotoxin to selectively kill cancer cells. This is considered to be a definition in terms of a result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result are however missing. Thus, none the independent claims meets the requirements of Article 6 PCT.

3.3 Although the application discloses a peptide in the insect RasGAP protein (WLWVTAHRTG) with homology to the WMWVTNLRTD sequence, no evidence is given that such a peptide also has the activity of enhancing the ability of a genotoxin to kill selectively cancer cells. No such evidence is given either for any of all the possible peptides (WxWVTxxRTx) other than for WMWVTNLRTD. Thus, subject-matter other than that concerning the peptides encoded by SEQ ID NOs: 1-4 (including WMWVTNLRTD) and to the peptide WLWVTAHRTG seems to lack support in the sense of Art. 6 PCT and does not seem to be sufficiently disclosed in the sense of Art. 5 PCT.

3.4 It appears from the description as a whole and in particular from table 2, that the presence of the sequence WMWVTNLRTD in the peptides claimed is an essential technical feature of the present invention. This essential technical feature is however not present in any of the independent claims. For these reasons the claims lack clarity according to Art. 6 PCT taken in combination with Rule 6.3 (b) PCT (see also PCT Preliminary Examination Guidelines Part II 5.4-5).

4. NOVELTY (Art. 33(2) PCT)

4.1 D4 discloses that a peptide consisting of amino acids 158 to 455 of RasGAP (N2 fragment, produced by RasGAP caspase cleavage), potentiates apoptosis and cell killing in genotoxin-treated tumor cells (HeLa cells; see page 5351, left-hand column, paragraph 2 to page 5354, right-hand column, paragraph 5, figures). The ability to enhance the ability of a drug to kill cells is an inherent property of the peptide. The compositions used in D4 are regarded as pharmaceutical compositions.

4.2 The pharmaceutical composition disclosed in D4 comprises a peptide (N2 domain of RasGAP), said peptide comprising the general amino acid sequence WXWVTXXRTX, and a genotoxin. The peptide referred to in claim **1** is "shorter than the N2 domain of RasGAP".

4.3 Thus, the subject-matter of independent claim **1**, appears to be new over the prior art (Article 33(2) PCT).

4.4 Accordingly, the novelty of the subject-matter of independent claims **22, 25 and 27-29**, relating to methods, uses or kits of the composition according to claim 1, and the subject-matter of claims dependent on said claims is also acknowledged (Article 33(2) PCT).

5. INVENTIVE STEP (Art. 33(3) PCT)

5.1 D4 is regarded as the closest prior art. The pharmaceutical composition disclosed in D4 comprises a peptide (N2 domain of RasGAP), said peptide comprising the general amino acid sequence WXWVTXXRTX, and a genotoxin. The **difference** of D4 with the application is that in the application, the peptide referred to in claim **1** is "shorter than the N2 domain of RasGAP" and that the peptide enhances the ability of the genotoxin to kill selectively cancer cells.

5.2 The **problem** to be solved by the present invention is the provision of a further pharmaceutical composition to kill selectively cancer cells. The **solution** of the application is to combine in a composition, a genotoxin with a peptide shorter than the N2 sequence of RasGapT and comprising the WMWVTNLRTD sequence, since said peptide enhances the ability of a genotoxin to kill selectively cancer cells.

5.3 This solution might be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

5.3.1 D1 discloses a peptide consisting of the sequence WMWVTNLRTD (P5, SEQ ID NO: 5), and peptides comprising the sequence WMWVTNLRTD (peptides P6 and P8) which are capable of inhibiting the transformation activity of the Ras protein (D1, example 3); D1 claims the use of said peptides in pharmaceutical compositions for the treatment of cancer.

5.3.2 D5 discloses that the inhibition of RasGAP (by a specific monoclonal antibody against the SH3 domain of RasGAP) induces apoptosis selectively in tumor cells (D5, e.g. abstract).

5.3.3 It appears that, although a skilled person would know from D4 that a peptide comprising the N2 domain of RasGAP enhances the apoptosis induced by genotoxins, said skilled person would not be motivated to chose specifically fragments of the N2 domain, even less to select the specific peptides disclosed in D1. The peptides in D1 are shown to have an activity of inhibiting Ras, but the activity of enhancing the ability of a genotoxin to kill cells is Ras independent (see e.g. D4). Thus, there is no incentive in any of the documents to induce a skilled person to combine the teachings of D4 and D5. Thus, a pharmaceutical composition comprising a combination of (i) a peptide shorter than N2 and comprising the subsequence WMWVTNLRTD and (2) a genotoxin for enhancing selective killing of cancer cells would not seem obvious over the available prior art.

5.3.4 Moreover, although D5 discloses an antibody against RasGap which induces apoptosis specifically in tumor cells, the skilled person would have no motivation to assume that a peptide as claimed in claim 1 would also have such an activity to selectively kill cancer cells.

5.4 Thus, it appears that the subject-matter of claim 1 can be regarded as inventive in the sense of Art. 33 (3) PCT.

5.5 Accordingly, the inventive step of the subject-matter of independent claims **22, 25 and 27-29**, relating to methods, uses or kits of the composition according to claim 1, and the subject-matter of claims dependent on said claims is also acknowledged (Article 33(3) PCT).

6. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

6.1 For the assessment of the present claims **25-28** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (Rule 39.1(iv) PCT).

CLAIMS

1. A pharmaceutical composition comprising a combination of

i) at least one peptide shorter than the N2 sequence of the RasGAP protein comprising the general amino acid sequence WXWVTXXRTX, or variants thereof, wherein X represents an amino acid,

ii) and a genotoxin,

characterized in that said at least one peptide enhances the ability of said genotoxin to kill selectively cancer cells.

2. The pharmaceutical composition of claim 1, characterized in that said at least one peptide shorter than the N2 sequence of the RasGAP protein comprises at least one amino acid sequence encoded by the DNA sequences SEQ ID No.1, SEQ ID No.2, SEQ ID No.3 or SEQ ID No.4.

3. The pharmaceutical composition of claims 1-2, characterized in that said at least one peptide shorter than the N2 sequence of the RasGAP protein comprises the amino acid sequence WMWVTNLRTD.

4. The pharmaceutical composition of claims 1-3, characterized in that said at least one peptide shorter than the N2 sequence of the RasGAP protein is in D-form and/or in a retro-inverso isomer form.

5. The pharmaceutical composition of claims 1 to 4, characterized in that said at least one peptide shorter than the N2 sequence of the RasGAP protein is conjugated to an agent which increases the cell accumulation of said at least one peptide.

6. The pharmaceutical composition of claim 5, characterized in that the agent is a cell membrane permeable carrier.

7. The pharmaceutical composition of claim 6, characterized in that the cell membrane permeable carrier is a peptide.

8. The pharmaceutical composition of claim 7, characterized in that the cell membrane permeable carrier peptide is in D-form and/or in a retro-inverso isomer form.

9. The pharmaceutical composition of claims 7-8, characterized in that the cell membrane permeable carrier peptide is an arginine rich peptide which is selected from the group comprising the HIV-TAT $_{48-57}$ peptide, the FHV-coat $_{35-49}$ peptide, the HTLV-II Rex $_{4-16}$ peptide and the BMV gag $_{7-25}$ peptide.

10. The pharmaceutical composition of claim 9, characterized in that the arginine rich peptide is the HIV-TAT $_{48-57}$ peptide.

11. The pharmaceutical composition of claims 1 to 10, characterized in that the genotoxin is selected from the group comprising alkylating agents, antimetabolites, DNA cutters, DNA binders, topoisomerase poisons and spindle poisons.

12. The pharmaceutical composition of claim 11, characterized in that alkylating agents are selected from the group comprising lomustine, carmustine, streptozocin, mechlorethamine, melphalan, uracil nitrogen mustard, chlorambucil, cyclosphamide, iphosphamide, cisplatin, carboplatin, mitomycin, thiotepa, dacarbazin, procarbazine, hexamethyl melamine, triethylene melamine, busulfan, pipobroman, mitotane and other platine derivatives.

13. The pharmaceutical composition of claim 12, characterized in that alkylating agents are selected from the group comprising cisplatine and other platine derivatives.

14. The pharmaceutical composition of claim 11, characterized in that the DNA cutter is bleomycin.

15. The pharmaceutical composition of claim 11, characterized in that toposiomerase poisons are selected from the group comprising topotecan, irinotecan, camptothecin sodium salt, daorubicin, doxorubicin, idarubicin, mitoxantrone, teniposide, adriamycin and etoposide.

16. The pharmaceutical composition of claim 15, characterized in that toposiomerase poisons are selected from the group comprising mitoxantrone and adriamycin.

17. The pharmaceutical composition of claim 11, characterized in that DNA binders are selected from the group comprising dactinomycin and mithramycin.

18. The pharmaceutical composition of claim 11, characterized in that spindle poisons are selected from the group comprising vinblastin, vincristin, navelbin, paclitaxel and docetaxel.

19. The pharmaceutical composition of claim 11, characterized in that antimetabolites are selected from the group comprising methotrexate, trimetrexate, pentostatin, cytarabin, ara-CMP, fludarabine phosphate, hydroxyurea, fluorouracyl, floxuridine, chlorodeoxyadenosine, gemcitabine, thioguanine and 6-mercaptopurine.

20. The pharmaceutical composition of claim 11, characterized in that the genotoxin is selected from the group comprising cisplatin, mitoxantrone and adriamycin.

21. The pharmaceutical composition of claims 1 to 20 for the treatment or prevention of cancer.

22. Use of the pharmaceutical composition of claims 1 to 20, in the preparation of a medicament for the treatment or prevention of cancer.

23. The use according to claim 22, characterized in that the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, liposarcoma, neuroendocrine tumor, mesothelioma, schwanoma, meningioma, adenocarcinoma, melanoma, leukemia, lymphoid malignancy, squamous cell cancer, epithelial squamous cell cancer, lung cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal

cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophageal cancer, a tumor of the biliary tract, and head and neck cancer.

24. The use according to claim 23, characterized in that the cancer is mesothelioma, testicular cancer or pancreatic cancer.

25. A method of treating or preventing cancer selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, liposarcoma, neuroendocrine tumor, mesothelioma, schwanoma, meningioma, adenocarcinoma, melanoma, leukemia, lymphoid malignancy, squamous cell cancer, epithelial squamous cell cancer, lung cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophageal cancer, a tumor of the biliary tract, and head and neck cancer, comprising administering a therapeutically effective amount of the pharmaceutical composition of claims 1 to 20 to a subject in need thereof.

26. The method of claim 25, characterized in that the cancer is mesothelioma, testicular cancer or pancreatic cancer.

27. A method for enhancing apoptosis selectively in a cancer cell, comprising contacting a cancer cell with the pharmaceutical composition of claims 1 to 20.

28. A method for selectively killing cancer cells comprising contacting a cancer cell with the pharmaceutical composition of claims 1 to 20.

29. A kit for treating or preventing cancer in a subject comprising the pharmaceutical composition of any of claims 1 to 20 optionally with reagents and/or instructions for use.

30. The kit of claim 29, further comprising a separate pharmaceutical dosage form including an additional anti-cancer agent selected from the group consisting of drugs, anti-epidermal growth factor receptors antibodies, radioimmunotherapeutic agents, and combinations thereof.